Autologous peripheral blood stem cell transplantation for acute myeloid leukemia

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Abstract: We report the results of a prospective, randomized phase 3 trial evaluating the use of autologous peripheral blood stem cell transplantation (ASCT) vs. intensive consolidation chemotherapy in newly diagnosed AML patients in complete remission (CR1). Patients with AML between 16-60 yrs of age in CR1 after two cycles of intensive chemotherapy and not eligible for allogeneic SCT were randomized between intensive chemotherapy with etoposide and mitoxantrone or ASCT following high-dose cyclophosphamide and busulfan. Of patients randomized (chemotherapy n=259; ASCT n=258), more than 90% received their assigned treatment arm. The two groups were comparable as regards prognostic factors. The ASCT group showed a markedly reduced relapse rate (58% vs. 70%, p=0.02) and better relapse free survival (RFS) at five years (38% vs. 29%, p= 0.065, HR 0.82 (0.66-1.1) with non-relapse mortality of 4% vs. 1% in the chemotherapy arm (p=0.02). Overall survival (OS) was similar (44% vs. 41% at 5 years, p=0.86) due to more opportunities for salvage with second-line chemotherapy and stem cell transplantation in patients relapsing on the chemotherapy arm. This large study shows a relapse advantage for ASCT as post remission therapy but similar survival since more relapsing patients on the chemotherapy arm were salvaged with a late transplantation for relapse. This trial is registered at http://www.trialregister.nl as NTR230 and NTR291.

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Abstract

We report the results of a prospective, randomized phase 3 trial evaluating the use of autologous peripheral blood stem cell transplantation (ASCT) vs. intensive consolidation chemotherapy in newly diagnosed AML patients in complete remission (CR1). Patients with AML between 16-60 yrs of age in CR1 after two cycles of intensive chemotherapy and not eligible for allogeneic SCT were randomized between intensive chemotherapy with etoposide and mitoxantrone or ASCT following high-dose cyclophosphamide and busulfan. Of patients randomized (chemotherapy n=259; ASCT n=258), more than 90% received their assigned treatment arm. The two groups were comparable as regards prognostic factors. The ASCT group showed a markedly reduced relapse rate (58% vs. 70%, p=0.02) and better relapse free survival (RFS) at five years (38% vs. 29%, p= 0.065, HR 0.82 (0.66-1.1) with non-relapse mortality of 4% vs. 1% in the chemotherapy arm (p=0.02). Overall survival (OS) was similar (44% vs. 41% at 5 years, p=0.86) due to more opportunities for salvage with second-line chemotherapy and stem cell transplantation in patients relapsing on the chemotherapy arm. This large study shows a relapse advantage for ASCT as post remission therapy but similar survival since more relapsing patients on the chemotherapy arm were salvaged with a late transplantation for relapse. This trial is registered at http://www.trialregister.nl as NTR230 and NTR291.

Introduction

Autologous bone marrow transplantation (ABMT) following marrow ablative chemotherapy or radiotherapy has originally been developed as an alternative to allogeneic stem cell transplants for patients with acute myeloid leukemia (AML) with no suitable donor. Several randomized studies in patients with AML in first complete remission (CR1) subsequently suggested reduced relapse rates following ABMT.[1-6]

However, ABMT has been associated with prolonged marrow aplasia and with an excess of non-relapse mortality.[2,3] As a result the relapse advantage of an autologous transplant was offset by enhanced toxicity and mortality which has precluded general acceptance of ABMT as post-remission treatment in AML.[1-6] In addition these studies with marrow auto grafts were hampered by the fact that only a minority of the allocated patients, actually underwent the transplantation.[7,8]

When hematopoietic growth factors provided the possibility to employ peripheral blood stem cells as the source of stem cells, autologous peripheral blood stem cell transplants (ASCT) offered the advantage of a markedly faster engraftment and accelerated hematological recovery as compared to marrow grafts.[9-11] The switch to ASCT was also expected to enhance compliance to protocol treatment so that a greater fraction of patients assigned to ASCT would indeed receive their intended transplantation. However, critical prospective evaluations of ASCT have remained remarkably scarce, and were performed in series with relatively small numbers of patients.[11,12]

Against this background, the Dutch-Belgian HOVON and Swiss SAKK leukemia cooperative groups set out to assess the clinical benefit of ASCT following high-dose cytotoxic therapy in a multicenter study in 517 patients with AML in CR1 following intensive anthracycline and cytarabine chemotherapy.[13,14] ASCT was prospectively compared to intensive consolidation chemotherapy with etoposide and mitoxantrone which have been reported to exert potent anti-leukemic effects.[13-15]

Materials and Methods

Study Design and Chemotherapy

Previously untreated patients with a confirmed diagnosis of AML were eligible for enrollment in the HOVON/SAKK AML-29 and AML-42 trials.[13,15] The age range for

the HOVON/SAKK AML-29 trial was 16 to 60 years and for the AML-42 trial 18 to 60 years. Patients with acute promyelocytic leukemia (APL) were eligible in the AML-29 trial but they were not in the AML-42 trial. Patients with another active cancer were not eligible, nor were patients with severe heart, lung, or neurological disease (Supplementary Information). Patients in CR1 after cycle 2 received consolidation with a third cycle of chemotherapy with etoposide (100 mg/m^2 on days 1 through 5) and mitoxantrone (10 mg/m^2 on days 1 through 5) in case of favorable cytogenetics and early CR after cycle I. Unfavorable risk patients were planned for an allogeneic stem cell transplantation and could be randomized in the study in case an allogeneic transplantation was not feasible. Intermediate risk patients were candidates for an HLA matched allogeneic stem cell transplantation if a donor was available and the patient fulfilled the age criteria for an allograft in their center. If allogeneic stem cell transplantation appeared no realistic option, patients could be randomized between ASCT or the third cycle of chemotherapy with etoposide and mitoxantrone. Conditioning before ASCT consisted of high-dose chemotherapy with busulfan (4 mg/kg orally days -4 through -7 and cyclophosphamide (60 mg/kg intravenously, days -2 and -3) followed by autologous peripheral blood stem cell re-infusion (see Supplementary Information).

This was an investigator-sponsored study with no pharma company involvement. The study was approved by ethics committees of the participating institutions and was conducted in accordance with the Declaration of Helsinki. All patients gave their written informed consent.

Prior Remission Induction Chemotherapy

Remission induction chemotherapy according the AML-29 and AML-42 protocols involved two cycles of combination chemotherapy.[13,14] Cycle 1 consisted of cytarabine (200 mg/m^2 on days 1 through 7) and idarubicin (12 mg/m^2 on days 6, 7, and 8). Cycle 2 consisted of cytarabine (1000 mg/m^2 every 12 hours on days 1 through 6) and amsacrin (120 mg/m^2 on days 4, 5, and 6). In the AML-42 protocol patients were also randomized between the aforementioned dose of cytarabine versus a more intensive cytarabine regimen (cycle 1 1000 mg/m^2 on days 1 through 5) and cycle 2 consisting of 2000 mg/m^2 twice daily on days 1, 2, 4, 6) as described.[13,14] In the AML-29 and part of the AML-42 trial patients were randomly assigned for induction to receive granulocyte colony stimulating factor (G-CSF) or no G-CSF during cycles 1 and 2 as described.[13]

Criteria For Response and Endpoints

CR, relapse and overall survival (OS) were previously defined.[13,15] Relapse-free survival (RFS) refers to the interval from randomization to the date of death, or the date of relapse. Time to hematopoietic recovery was measured from the end of chemotherapy application both for patients treated according to chemotherapy cycle III or to the transplantation group to the time when the neutrophil and the platelet counts reached values of 0.5 x 10^9/l and 50 x 10^9/l, respectively.

Statistical Methods

Design and Randomization

RFS was the primary endpoint. At the onset of this randomization in the AML-29 study it was clear that the number of patients randomized between third chemotherapy course and ASCT would not be sufficient to answer the question with sufficient power. Therefore the randomization was planned to be continued in the

successive AML-42 study. Randomization was closed in 2006. After an additional follow up of 3.5 yrs 343 events (relapse or death in CR1) have been observed in both groups together. This number of events gives a power of 71% for the detection of a significant difference if the true hazard ratio of failure in the ASCT group compared with the chemotherapy group would be 0.76, which corresponds with an increase in the 5-year RFS from 30 to 50%.

Randomized assignments to study groups were balanced with the use of a biased-coin minimization procedure as described (see Supplementary Information),

Analysis

All analyses were performed according to the intention-to-treat principle, irrespective of patients compliance with the protocol, but 12 ineligible patients randomized between cycle III (n=5) and ASCT (n=7) were excluded: patients with acute promyelocytic leukemia (n=6); never reached CR1 (n=2); relapsed before randomization (n=2); incorrect diagnosis (n=2).

Cox regression analysis was used to estimate the effect of treatment group and covariates on RFS and OS (secondary endpoint). The possible heterogeneity of the treatment effects in subgroups was explored in post hoc analyses by estimation of the hazard ratios for each subgroup, together with 95% confidence intervals, and tests for interaction. A limited number of subgroup classifications were considered: cytogenetic risk category (favorable, intermediate, or unfavorable), age, WHO performance status (0, or 1 or 2), presence of extra-medullary disease and white blood cell count ($\leq 20 \times 10^9$ /l) at diagnosis, and early (CR after cylce I) or late (CR after cycle II) CR1. P-values <0.05 were considered statistically significant, except for the tests for interaction with subgroups, where <0.01 was used because of multiple tests performed.

Results

Between 1995 and 2006 2017 patients at diagnosis were enrolled in the AML-29 and AML-42 trial for remission induction treatment. After 2-courses of chemotherapy induction therapy, 76% of the patients were in CR1 (Table 1). The recommended choice of consolidation treatment in the protocol according to the cytogenetic risk stratification (see Methods) resulted in the randomization of 34% of patients while 23% of patients went straight to consolidation chemotherapy (cycle III) and 27% were consolidated in CR1 with an allogeneic SCT depending on the availability of a HLA matched donor and clinical eligibility criteria (age, co-morbidity). Two percent of patients received an ASCT without randomization and 15% did not receive further therapy in CR1 due to early relapse or prolonged hypoplasia (Table I). Thus, of 517 randomized patients 259 were assigned to consolidation chemotherapy cycle III and 258 patients to ASCT. Median follow-up of patients alive is 106 months (range 13-177). Nine patients in the chemotherapy group and 7 patients in the ASCT have been lost to follow-up between 1 and 12 years. The two treatment groups were matched with respect to age, cytogenetic risk, types of induction therapy (Table 2). Ninety-three percent of the patients randomized to consolidation chemotherapy received the planned chemotherapy according protocol and 91% of the patients assigned to ASCT actually received the autologous transplant (Table 3).

Outcome following chemotherapy or ASCT

The ASCT treatment group showed a trend towards better RFS than the chemotherapy group (38% vs. 29% at 5 years, p=0.065, HR 0.82 (0.66-1.1) (Table 3;

Figure 1). In the ASCT group 156 patients had recurrence of AML, while 187 patients relapsed in the chemotherapy group, corresponding with an actuarial relapse rate at 5 years of 58% and 70%, respectively (p=0.02, Table 3). Non-relapse mortalities (a measure of treatment-procedure related deaths) were estimated at 4% and 1% (at 5 yrs) in the ASCT and chemotherapy groups (p=0.02). OS did not differ between both treatment arms (44% vs. 41%, p=0.86). Second line anti-leukemic treatment was applied to 116 (74%) of the 156 relapsing patients in the ASCT arm which involved ASCT (n=2, 1% of recurrences), allogeneic SCT (n=27, 17%) and chemotherapy (n=87, 55%). In contrast 150 of 187 (80%) relapsing patients in the chemotherapy group were treated in second line with ASCT (n=27, 14%), allogeneic SCT (n=47, 25%) or chemotherapy (n=76, 40%). Thus a considerably greater proportion of patients following relapse in the consolidation chemotherapy group had the possibility for salvage with autologous or allogeneic stem cell transplantation (39% versus 18%). Second complete remissions were attained in 27% of the relapsed patients in the ASCT group and 47% in the chemotherapy group resulting in long term survival of 7% and 15% for patients with relapse in the ASCT group and the chemotherapy group, respectively.

Hematological Recovery And Treatment Related Toxicity

A significantly enhanced recovery of peripheral blood granulocyte count was seen following ASCT as compared to consolidation chemotherapy (Figure 2). Thirty-two percent of ASCT patients reached neutrophil counts of >0.5 x 10^9/l at day 14 and 88% on day 28 after transplant as compared to 1% and 42% respectively for patients consolidated with chemotherapy (p<.001). Platelet recovery demonstrated a biphasic pattern; in the first month after end of treatment the platelet recovery rate to >50 x 10^9/l was slightly faster in the ASCT group (p=0.79). However, for the patients who

had not recovered by that time the platelet recovery proceeded at a slower rate in the ASCT group (p<.0001, fig 2) A similar pattern was seen with respect to time to platelet transfusion independency; the median time to transfusion independency was comparable between both groups, 24 days vs. 23 days, but after that the duration was longer in the ASCT group (p=0.003). In the ASCT group the incidences of grade 3 and 4 bleedings and grade 3 and 4 infections were not different (see Supplementary Information S1). However, an increased incidence of fever of unknown origin (37% versus 21%, p<.001), gastro-intestinal (72% versus 29%, p<.001), hepatic (18% versus 6%, p<.001) and neurological (11% versus 4%, p=0.004) grade 2-4 adverse events were noted in the ASCT group.

Prognostic Factors And Subgroup Analysis

Table 4 shows the actuarial 5 year probabilities of RFS and OS and the hazard ratios in relation to clinical and hematological factors and according to treatment group. Increasing age was associated with a reduced RFS (P=0.01) and OS (P<0.001). Presence of extra-medullary disease at diagnosis also correlated with lower RFS (P=0.016) and OS (P=0.21). Cytogenetics showed particularly strong relationships with RFS and OS. The ASCT group showed better RFS than the chemotherapy group (at 5 yrs 38% vs. 29%), but this difference was not statically significant (p=0.065). However, if the patients of the monosomal karyotype with very poor RFS in both arms were excluded, the improvement in RFS for the ASCT arm was more pronounced (p=0.014). Patients attaining late CR (i.e. after induction cycle II) had a considerably lower RFS and OS (P<.001) than those in CR already after cycle I.

In order to explore for a possible differential effect of ASCT treatment on outcome in any of the subgroups defined by the aforementioned factors, the effect of treatment was estimated separately by HR for RFS and OS with associated confidence

intervals combined with tests for interaction. In none of the latter analyses the test for interactions were significant (all P-values for these tests >0.10), including G-CSF priming and Ara-C dose applied.

Discussion

Randomized transplantation studies about ABMT in AML in CR1 had demonstrated reduced relapse rates in association with considerable procedural limitations including low treatment compliance, delayed hematological regeneration and increased non-relapse mortality.[1-6] The present study demonstrates that these hurdles can largely be overcome. Autografts were successfully collected in a high number of patients and a high proportion of randomized patients did indeed receive their assigned treatment which enhanced the ability of evaluating the true value of ASCT according to intention to treat. The results show an advantage for ASCT as post-remission therapy in terms of relapse rate (57% versus 70% at 5 yrs, p=0,002) and with a higher RFS (39% versus 29% at 5 yrs, p=0,065). The OS was only slightly better after ASCT (44% vs. 41% at 5 yrs), but this difference was far from statistically significant (p=0.86). It should be noted that the similar OS value in the two groups was due to a higher proportion of successful salvage treatments, especially ASCT and allogeneic SCT, given after relapse in the chemotherapy group compared to the ASCT group.

Despite a marked accelerated granulocyte recovery in the ASCT arm more side effects were noticed likely related to more intensive chemotherapy and resulting in a treatment related mortality of 4% in the ASCT arm vs. 1% in the chemotherapy arm.

An important question is whether the choice of the remission induction therapy and the third cycle of mitoxantrone-etoposide for remission consolidation furnish a proper comparison as regards the value of ASCT. In the current study ASCT was given after

two cycles of induction therapy with cytarabine at conventional and intermediate dose levels and compared with the same treatment plus a third cycle of mitoxantrone-etoposide. Does the latter treatment that served as a control represent a proper comparative reference? It has been thought for some time that a consolidation treatment with high-dose cytarabine (HD-Ara-C) is optimal for young and middle aged adults with acute myeloid leukemia.[16] However, while an earlier study had shown superiority of 3000 mg/m^2 over 400 mg/m^2 cytarabine it did not furnish any direct evidence supporting the need of four cycles of HD-Ara-C[16]. Accumulating data suggest that multiple cycles of HD-Ara-C and dose levels of cytarabine above 1000 mg/m^2 whether applied in induction or consolidation are of limited value. In one randomized trial two postremission cycles of standard-dose Ara-C versus one HD-Ara-C schedule made no difference. [17] In an additional study three HD-Ara-C cycles applied postremission did not yield better outcome than one cycle.[18] A large recent Japanese study has recently reinforced the notion that standard dose levels of cytarabine applied as postremission therapy are not inferior to high dose levels.[19] Our group has previously employed and applied in the standard arm of the current study an intensive treatment program involving a first induction cycle of standard-dose Ara-C, a second cycle of intermediate-dose Ara-C and one third final consolidation cycle, and we have reported outcome in a range similar to that after four cycles of HD-Ara-C. [13, 15, 20]

Our study does not allow a critical analysis of the value of ASCT in cytogenetically defined favorable risk and unfavorable risk subsets of AML patients because of the limited numbers of patients studied. However, the results are in line with other studies demonstrating no advantage of ASCT in patients with monosomal karyotype.[17-19] Excluding these patients from the analysis resulted in a significant advantage in RFS for the ASCT arm (p=0.01).

Irrespective of the choice of post-remission treatment, i.e. ASCT or chemotherapy, relapse of leukemia remains the predominant cause of treatment failure. This is reflected by the profound impact of karyotype subtype on RFS and OS. During the time span of the study, a number of insights have evolved as regards the therapeutic management of AML which may impact on the future enforcement of ASCT. For instance, within the cytogenetic defined intermediate risk group, subgroups are defined with favorable and unfavorable outcome based on somatic gene mutations in CCATT enhancer binding protein alpha (CEBPA), Nucleophosmin-1 (NPM1) and Fms-like tyrosine kinase 3 (FLT3).[21-24] One study has already demonstrated that the subset of patients with *NPM*1^{+} mutations without *FLT3*-internal tandem duplications (*FLT3-ITD*) derive no survival benefit from allogeneic SCT.[24] Direct outcome data as regards ASCT in these and other genotypes are currently not available but one might assume that the value of ASCT in these genotypic subsets will follow the cytogenetic prognostic analogies as has previously been demonstrated for allogeneic SCT.[25] Allogeneic transplantation following reduced dose-intensive conditioning is nowadays quite commonly used in patients with AML because of reduced early toxicities but it involves a greater relapse rate than myelo-ablative regimens.[26-29] The ability of ASCT to suppress relapse in CR1 suggests that ASCT might also have merits in AML-CR1 as a an adjunct regimen prior to allogeneic SCT. ASCT appears to minimize the leukemic burden and stabilize remissions and thus it might create better conditions and allow more time for graft versus-leukemia control. Finally, the remarkably low procedural mortality following ASCT that we report here after prolonged follow up, makes ASCT also potentially attractive for other subgroups, e.g. for favorable risk AML where it might contribute to preventing relapse.

Author's Disclosures of Potential Conflicts of Interest

The authors indicated have no potential conflicts of interest

Author Contributions

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Final approval of manuscript: all authors

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Table 1. Treatment results of patients treated according HOVON-29 and HOVON-42 protocol

	Cytogenetic risk group			
	Favorable	Intermediate	Unfavorable/Very unfavorable	Total
Patients entered for induction	n=233	n=1437	n=347	n=2017
In CR after cycle II	205 (88%)	1134 (79%)	193 (56%)	1532 (76%)
Not randomized				
No consolidation	30 (15%)#	166 (15%)#	33 (17%)#	229 (15%)#
Consolidation				353 (23%)
Chemotherapy cycle III	116 (57%)	215 (19%)	22 (11%)	24 (2%)
ASCT	3 (1%)	20 (2%)	1 (1%)	409 (27%)
Allogeneic SCT	17 (8%)	308 (27%)	84 (44%)	
Randomized for consolidation				
Chemotherapy cycle III	21 (10%)	210 (19%)	28 (15%)	259 (17%)
ASCT	18 (9%)	215 (19%)	25 (13%)	258 (17%)

remaining percentages refer to percentage of patients in CR after cycle II.

Cytogenetic risk group: for details see legends Table 1. AML of favorable risk had core binding factor abnormalities: t(8;21) (q22;q22), inv(16)(p13.1;q22), or t(16;16)(p13.1;q22). The “very unfavorable” risk category had a monosomal karyotype as defined.[30,31] The unfavorable risk AML’s were those without a monosomal karyotype or core-binding abnormalities, but with complex abnormalities[15], t(6;9), t(11,19), t(9;22), 11q23.3q, inv(3),5q-,7q-, -5 or -7. AML without cytogenetic abnormalities or with loss of an X or Y chromosome as the only abnormality were classified as “normal cytogenetics” (“CN”) and AML with any other cytogenetic abnormalities were classified as “CA rest”. CN and CA-rest were considered as intermediate risk.

Table 2. Patients with AML in complete remission randomized to consolidation with chemotherapy (cycle III) or autologous stem cell transplantation (ASCT): demographics at diagnosis and preceding remission induction therapy

	Cycle III	ASCT
Total	259 100%	258 100%
Male sex	126 49%	132 51%
Age (years)		
Median	47 yr	49 yr
16-40	98 38%	79 31%
41-50	57 22%	60 23%
50-61	104 40%	119 46%
WBC at diagnosis [x10^9/l]		
<=20	138 53%	125 49%
20-100	89 34%	96 37%
>100	32 12%	36 14%
FAB type		
M0	7 3%	12 5%
M1	55 21%	64 25%
M2	70 27%	62 24%
M4	50 19%	60 23%
M5	53 20%	46 18%
M6	10 4%	6 2%
M7	0	2 1%
RAEB	3 1%	2 1%
RAEB-t	4 2%	3 1%
Unknown	7 3%	1 0%
Secondary leukemia	11 4%	18 7%
Extra-medullary disease	37 14%	31 12%
Cytogenetics		
Favorable		
t(8;21)	4 2%	5 2%
inv(16)	17 7%	13 5%
Intermediate	195 70%	213 72%
CN-X-Y	138 53%	145 56%
CA Rest	67 26%	68 26%
Unfavorable	16 6%	16 6%
Vey unfavorable (Monosomal karyotype)	17 7%	11 4%
Not determined	16 6%	16 6%
Remission induction with G-CSF priming*		
No	195 75%	191 74%
Yes	64 25%	67 26%
Remission induction with cytarabine at *		
Intermediate-dose level	51 58%	45 54%
High-dose level	37 42%	38 46%
CR reached after #		
Cycle I (early CR)	210 81%	203 79%
Cycle II (late CR)	49 19%	55 21%

Third cycle of consolidation chemotherapy (cycle) vs. autologous stem cell transplantation (ASCT); WBC: white blood cell count; *as described in Methods remission induction therapy varied according to a randomized study for remission induction that compared two dose levels of cytarabine in remission induction and yes versus no G-CSF priming. #Achieved after 1 or 2 induction chemotherapy.

Favourable: core binding factor abnormalities: t(8;21) (q22;q22), inv(16)(p13.1;q22), or t(16;16)(p13.1;q22). Unfavorable includes here the patients with an unfavorable karyotype and the patients with a monosomal karyotype. Intermediate: all other patients including those without cytogenetic abnormalities.

Table 3. Outcome of patients with AML in first complete remission randomized to consolidation chemotherapy (cycle iii) or autologous stem cell transplantation (ASCT)

	Cycle III	ASCT
Total	259 100%	258 100%
Consolidation treatment		
None	6 2%	11 4%
Chemo	240 93%	10 4%
ASCT *	9 3%	236 91%
AlloSCT **	4 2%	1 0%
Relapse-free survival (actuarial 5 years %)		P=0.065
Median [months]	11	14
RFS	69 29%	89 38%
Relapse	187 70%	156 58%
Death in CR1	3 1%	13 4%
Overall survival (actuarial 5 years %)		P=0.86
Alive	99 41%	101 44%
Dead	160 59%	157 56%
Cause of death		
AML	119 46%	114 44%
Pneumonitis	8 3%	6 2%
Other infections	12 5%	8 3%
Hemorrhage	4 2%	4 2%
GvHD	4 2%	4 2%
Secondary malignancy	-	1 0%
Cardiac	-	2 1%
Other	13 5%	18 7%

Numbers of patients (and %) per randomized treatment, i.e. consolidation cycle III or ASCT

Chemo: chemotherapy; *ASCT: autologous stem cell transplantation; **AlloSCT: allogeneic SCT; RFS: relapse free survival; GvHD: graft versus host disease.

Table 4. Prognostic factors and test for interaction with treatment arm

			5 year RFS %			Cox regression RFS B vs A				5 year OS %			Cox regression OS B vs A		
	Npat	Event	All	A	B	HR	95%CI	P-value	Dead	All	A	B	HR	95% CI	P-value
	#	#	%	%	%				#	%	%	%			
Total	517	359	33	29	38				317	42	41	44			
Age			P=.010					P-int=.22		P<.001					P-int=.34
<=40	177	114	37	29	47	0.65	0.44-0.95	.025	89	52	47	57	0.85	0.56-1.30	.46
41-50	117	72	38	30	46	0.73	0.46-1.16	.18	68	43	39	48	0.82	0.51-1.33	.43
>50	223	173	28	29	27	0.98	0.73-1.32	.90	160	35	35	34	1.17	0.86-1.60	.33
Extra-medullary disease			P=.016					P-int=.25		P=.21					P-int=.85
No	449	304	35	31	39	0.87	0.69-1.08	.21	272	43	41	45	1.03	0.81-1.31	.79
Yes	68	55	22	16	28	0.61	0.36-1.05	.076	45	37	35	38	0.98	0.54-1.76	.93
Cytogenetics			P<.001					P-int=.13		P<.001					P-int=.20
Favorable	39	20	49	33	67	0.39	0.15-1.02	.055	11	72	71	72	1.03	0.31-3.36	.97
Intermediate	393	271	35	32	38	0.87	0.69-1.11	.27	244	43	40	45	1.00	0.78-1.28	.99
Unfavorable	25	20	20	18	21	0.77	0.32-1.86	.56	18	28	27	29	0.99	0.39-2.52	.99
Very unfavorable	28	28	0	0	0	1.76	0.82-3.78	.15	27	4	6	0	2.49	1.15-5.41	.021
CR reached after			P<.001					P-int=.35		P<.001					P-int=.29
Cycle I	413	275	37	32	42	0.78	0.61-0.99	.037	241	45	43	48	0.95	0.74-1.23	.72
Cycle II	104	84	20	18	21	0.97	0.63-1.49	.89	76	31	31	32	1.25	0.79-1.96	.34

A: Chemo group, B: ASCT group; For cytogenetic risk classification: see Table 1. HR Hazard ratio estimate, CI confidence interval.

P-values Cox regression: likelihood ratio test for difference between treatment groups within row-subgroup.

The P-values in the “All” columns are for tests for trend or difference between the factor and RFS or OS

The P-values for the test of interaction between the factor and treatment group are indicated by P-int.

Figure Legends

Figure 1.

Overall survival (OS) and relapse free survival (RFS) of patients with AML in first complete remission randomized to autologous stem cell transplantation (ASCT) or consolidation chemotherapy.

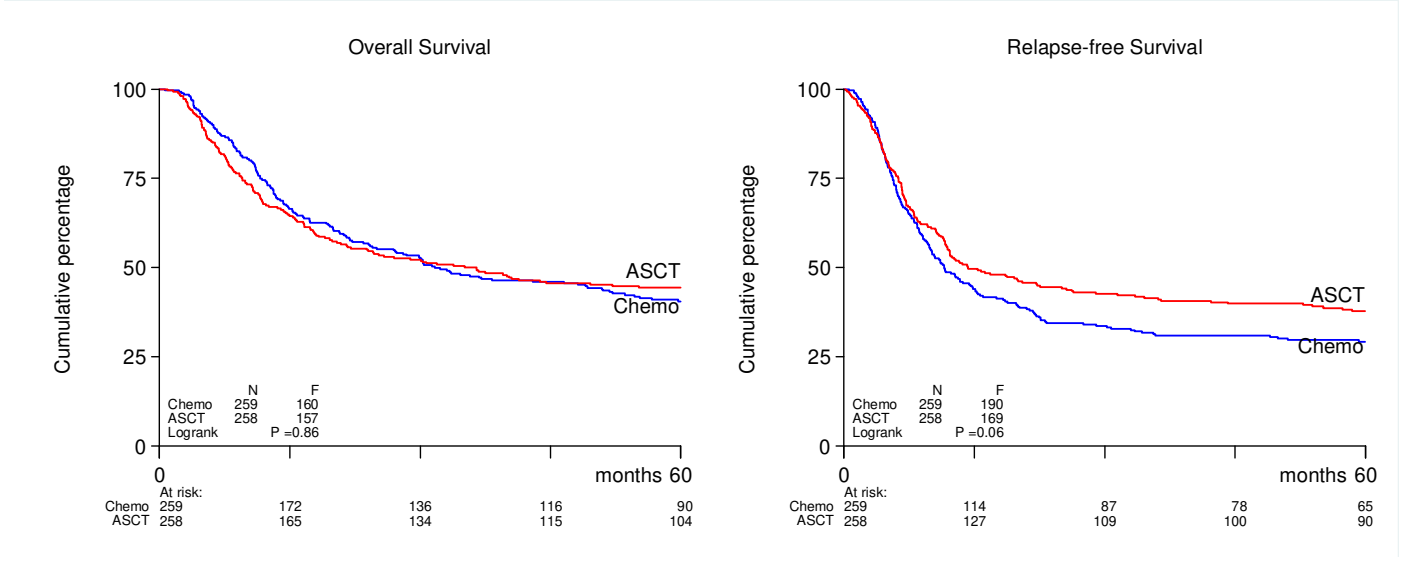

Figure 2.

Recoveries of absolute neutrophil counts (ANC, 0.5 x 10^9/L) and platelet counts (50 x 10^9/L) following autologous stem cell transplantation or consolidation chemotherapy. Recovery was measured from the date of transplant in the ASCT group and for comparability from the last date of cycle III in the chemotherapy group. The calculations have been restricted to patients treated according to allocated treatment.